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ORIGINAL ARTICLE

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Fever in neutropenia in children and adolescents: Evolution over time of main characteristics in a single center, 1993–2001

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The results of this study have been presented in part at the 35th Annual Congress of the International Society of Paediatric Oncology (SIOP) in October 2003 in Cairo.

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Abstract *Goals of work:* To assess the evolution over time of main characteristics of episodes of fever in severe chemotherapy-induced neutropenia (FN) in children and adolescents with cancer treated for FN following nonmyeloablative chemotherapy, to compare the results with the experiences of other centers, and to assess the impact of the changes found on management of FN and on risk prediction rules. *Patients and methods:* Retrospective cohort study of all children and adolescents up to 18 years presenting with FN in a single pediatric oncology unit between 1993 and 2001. *Main results:* In 132 patients, 364 episodes of FN were reported. The relative incidence of FN increased significantly over time in patients with precursor B-cell acute lymphoblastic leukemia (PBC-ALL), reflecting the increased intensity of chemotherapy. At presentation with FN, the proportions of patients (1) with PBC-ALL versus other malignancies, (2) with other malignancies being in complete remission, (3) with a central venous catheter, and (4) with shaking chills all significantly increased over time (overall proportions, 64%, 60%, 50%, and 5%, respectively; $p < 0.001$ for all). In 337 (93%) episodes, ceftriaxone plus amikacin was used as empirical broad spectrum antimicrobial therapy. *Conclusions:* This study demonstrates that some characteristics of FN, though not necessarily its management, change over time, implying regular update of risk prediction rules. In contrast to other centers, the first-line antimicrobial therapy did not need modification because of changing resistance patterns.

Keywords Fever in neutropenia · Chemotherapy · Risk prediction · Antibiotic resistance

Introduction

Fever in severe chemotherapy-induced neutropenia (FN) is the most frequent potentially life-threatening complication in adult and pediatric oncology. Compared to adults, children with FN are less likely to have a clinically apparent site of infection, but the overall proportion of detectable bacteremia is similar, ranging from 10% to 30% [2, 14]. The incidence of significant bacterial infections, including bacteremia, positive urine culture, pneumonia, or unexpected death from infection [16] is higher, ranging from 20% to 55% [2, 16]. Despite the fact that only a minority of episodes of FN are caused by detectable bacterial infections, immediate empirical treatment with broad spectrum antibiotics is mandatory in all episodes of FN in children. Without such therapy, usually administered in an inpatient setting, case-fatality rates up to 80% in the case of gram-negative infections would be expected [2].

Recently, rules for the prediction of episodes of FN at low risk of complications have been established not only in adult oncology [17] but also in retrospective [1, 4, 8, 14] and prospective [11, 16, 18, 19, 22, 23] pediatric studies, though there is no multinationally accepted risk

prediction rule in pediatric oncology. The purpose of these risk prediction rules is to allow for outpatient management and oral antimicrobial therapy in selected low-risk episodes of FN.

Information on possible changes over time of characteristics in pediatric FN are contradictory [6, 15, 21, 24, 28]. Such changes can require adaptation of the management of FN itself, e.g., the choice of empirical broad-spectrum antimicrobial therapy and of rules predicting low-risk episodes of FN [12]. The primary purpose of this study was to assess the evolution over time of main characteristics of epidemiology, presenting signs and symptoms, management, and outcome of episodes of FN in a single tertiary care center of pediatric oncology. Secondary purposes were to compare this evolution with results published by other centers and to assess the potential implications on management of FN itself and on risk-prediction rules in pediatric FN.

Patients and methods

Study design

A retrospective, single-site, cohort study was conducted at the Division of Pediatric Hematology and Oncology, University Children's Hospital, University of Bern, Bern, Switzerland. Information on all children and adolescents diagnosed with a neoplasm between January 1, 1993 and December 31, 2001, and aged up to 17 years at diagnosis was extracted from an electronic database. Charts were screened for episodes of FN occurring within the same time interval and up to the age of 18 years.

Patients/episodes

An episode of FN was defined as an axillary temperature $\geq$38.5°C persisting $\geq$2 h or as a single temperature measurement of $\geq$39.0°C in a child with severe neutropenia, i.e., an absolute neutrophil count (ANC) $\leq 0.5\times10^9$/l or an ANC $\leq 1.0\times10^9$/l and supposed to decline [2]. Repeated episodes per patient were allowed. Episodes of FN due to bone marrow involvement by the disease itself, e.g., at the time of diagnosis of leukemia, and episodes following myeloablative therapy were excluded. Information on characteristics at presentation with FN and on its management and outcome were collected. Bacteremia was defined as at least one positive blood culture bottle irrespective of the species detected, i.e., including coagulase-negative staphylococci (CoNS). Details of data collection have been described elsewhere [4]. During the time period studied, there was no antibiotic prophylaxis given [9], with the exception of trimethoprim-sulfamethoxazole (5 mg/kg trimethoprim + 25 mg/kg sulfamethoxazole per day, 3 days per week) as prophylaxis against *Pneumocystis jiroveci* pneumonia. Most patients were treated according to protocols of the Pediatric Oncology Group.

Statistical methods

The evolution of characteristics of FN over the time period studied was assessed graphically and with the test for trend in ordered Poisson rates for incidences, the Cochran-Armitage test for binary variables, and the Jonckheere-Terpstra test for continuously measured variables, respectively [25]. Two-tailed exact tests were used throughout. Because of the exploratory nature of the study [3], no formal corrections for multiple testing were made, but only p values <0.01 were considered significant. Repeated episodes per patient were allowed without formally applying the corresponding statistical techniques. Analyses concerning only the first episode of FN per patient were performed wherever appropriate. Diagnosis of a neoplasm and presentation with FN were restricted to the same period of time. In order to correct for possible influences of this fact, data concerning the years 1993 or 2001 were excluded from analysis wherever appropriate in the epidemiological section. Because of the high proportion of episodes of FN in patients with precursor B-cell acute lymphoblastic leukemia (PBC-ALL), comparisons between patients with PBC-ALL versus all other diagnoses were performed where appropriate. The StatXact 5.0.3 (CYTEL Software Corp., Cambridge, MA, USA) software was used for exact tests.

Results

Epidemiology

Between January 1, 1993, and December 31, 2001, 385 patients were diagnosed with a neoplasm. (See Fig. 1 for the spectrum of diagnoses.) Of these, 290 (75%) were treated with chemotherapy. Both the incidences of patients diagnosed with a neoplasm and of patients treated with chemotherapy were decreasing over time (Table 1). The incidence of patients diagnosed with PBC-ALL remained constant, while the number of new patients with other malignancies decreased. In 132 (46%) of the 290 patients treated with nonmyeloablative chemotherapy, 364 episodes of FN were reported. The median number of episodes of FN per patient was two. The proportion of patients with chemotherapy and at least one episode of

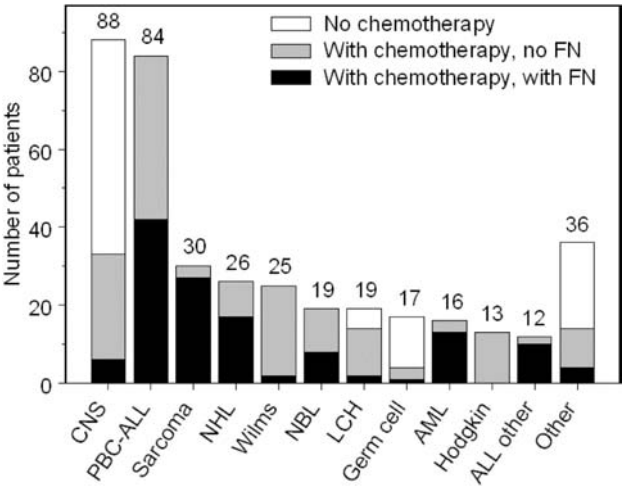

Fig. 1 Diagnoses of new patients treated in our center between 1993 and 2001. *CNS* tumors of the central nervous system, *PBC-ALL* precursor B-cell acute lymphoblastic leukemia, *NHL* non-Hodgkin lymphoma, *LCH* Langerhans cell histiocytosis, *AML* acute myeloid leukemia. *ALL other* acute lymphoblastic leukemia other than PBC-ALL

Table 1 Epidemiology. *PBC-ALL* precursor B-cell acute lymphoblastic leukemia, *FN* episode of fever in severe chemotherapy-induced neutropenia, *n.s.* not significant, i.e., p $\geq$0.01

Characteristic	Sample size	Statistic	*p* value
Patients diagnosed with neoplasm	385	−3.00 [a]	0.003
Patients treated with chemotherapy	290	−3.14 [a]	0.002
PBC-ALL	84	−1.01 [a]	n.s.
Other diagnoses	206	−3.08 [a]	0.002
Absolute incidence of FN[b]	335	0.38 [a]	n.s.
Patients with chemotherapy and at least one FN	132	−0.87 [c]	n.s.
Number of FN per patient treated with chemotherapy[d]	264	3.36 [a]	<0.001
In patients with PBC-ALL[d]	74	5.06 [a]	<0.001
In patients with other diagnoses[d]	190	0.23 [a]	n.s.

[a] Standardized test statistic of the exact test for trend in ordered Poisson rates
[b] Data from 1993 excluded from analysis: 29 episodes
[c] Standardized test statistic of the exact Cochrane-Armitage test for trend in binary data
[d] Data from 2001 excluded from analysis: 26 patients, ten of them with PBC-ALL

Table 2 Characteristics at presentation with episode of fever in severe chemotherapy-induced neutropenia (FN). *PBC-ALL* precursor B-cell acute lymphoblastic leukemia, *G-CSF* granulocyte colony-stimulating factor, *n.s.* not significant, i.e., p $\geq$ 0.01

Characteristic	Sample size	Overall median/%	Statistic	*p* value
Age at first FN (years)	132	6.6	−0.21 [a]	n.s.
Gender at first FN (female0	132	39%	0.60 [b]	n.s.
Diagnosis of PBC-ALL, only first FN	132	32%	1.91 [b]	n.s.
Diagnosis of PBC-ALL	364	34%	6.49 [b]	<0.001
Time since diagnosis at first FN (months)	132	1.4	0.77 [a]	n.s.
Complete remission	364	60%	4.43 [b]	<0.001
PBC-ALL	123	80%	1.07 [b]	n.s.
Other diagnoses	241	49%	3.77 [b]	<0.001
Bone marrow free of malignancy	364	85%	−2.11 [b]	n.s.
Low intensity of chemotherapy [c]	364	26%	2.61 [b]	0.008
Prophylaxis with G-CSF	363	52%	2.40 [b]	n.s.
Central venous catheter inserted	364	50%	6.35 [b]	<0.001
Yet hospitalized before developing FN	364	15%	−1.99 [b]	
Shaking chills observed	362	6%	3.16 [b]	0.001
Maximum temperature within first 2 h (°C)	359	39.1	1.71 [a]	n.s.
General appearance nontoxic	304	26%	1.06 [b]	n.s.
Shaking chills observed	362	6%	3.16 [b]	0.001
Severe oral mucositis requiring i.v. hydration	324	2%	1.42 [b]	n.s.
Independent comorbidity requiring hospitalization	364	20%	1.50 [b]	n.s.
Radiologically defined pneumonia	364	3%	1.98 [b]	n.s.
Hemoglobin level (g/l)	362	88	0.92 [a]	n.s.
Leukocyte count (10^9/l)	362	0.50	−2.78 [a]	0.006
Absolute neutrophil count (10^9/l)	174	0.06	0.78 [a]	n.s.
Platelet count (10^9/l)	356	18	0.74 [a]	n.s.
Serum level of C-reactive protein (mg/l)	329	48	2.43 [a]	n.s.

[a] Standardized test statistic of the exact Jonckheere-Terpstra test
[b] Standardized test statistic of the exact Cochrane-Armitage test for trend in binary data
[c] Low intensity chemotherapy: comparable to continuation therapy in Precursor B-cell acute lymphoblastic leukemia

FN remained stable over time, as was the absolute incidence of FN. The relative incidence, i.e., the number of episodes of FN per patient treated with chemotherapy, however, increased significantly in patients with PBC-ALL but not in patients with other malignancies.

Characteristics at presentation with FN

Episodes of FN in patients with PBC-ALL increased significantly over time, while episodes in patients with other malignancies decreased (Table 2). This evolution was identical in patients with and without relapse (data not shown). In patients with malignancies other than PBC-ALL, the proportion of patients being in complete remission at presentation with FN increased over time. The proportions of patients presenting with FN (1) after a low intensity chemotherapy, i.e., comparable to continuation therapy in PBC-ALL; (2) with a central venous catheter; and (3) with shaking chills, all increased significantly over time. The median leukocyte count decreased significantly over time. The ANC at presentation remained stable. It was determined in only 174 (48%) of the episodes, since no differentiation was performed with

Table 3 Management of Episode of fever in severe chemotherapy-induced neutropenia (FN). *n.s.* not significant, i.e., p $\geq$0.01

Characteristic	Sample size	Overall median / %	Statistic	*p* value
Number of blood cultures performed per FN	364	4	6.02 [a]	<0.001
Episodes with at least one urine culture performed	364	59%	3.02 [b]	0.002
Highest serum level of C-reactive protein (mg/l)	358	87	4.51 [c]	<0.001
Ceftriaxone plus amikacin as first-line therapy	364	93%	0.79 [b]	n.s.
Duration of i.v. antimicrobial therapy (days)	363	5	0.95 [c]	n.s.
Duration of hospitalization (days)	364	5	–1.32 [c]	n.s.
Leukocyte count at discharge (10^9/l)	320	2.00	–0.51 [c]	n.s.
Absolute neutrophil count at discharge (10^9/l)	261	0.77	–0.29 [c]	n.s.
Continued i.v. antimicrobial therapy at discharge	355	18%	3.08 [b]	0.002

[a] Standardized test statistic of the exact test for trend in ordered Poisson rates
[b] Standardized test statistic of the exact Cochrane-Armitage test for trend in binary data
[c] Standardized test statistic of the exact Jonckheere-Terpstra test

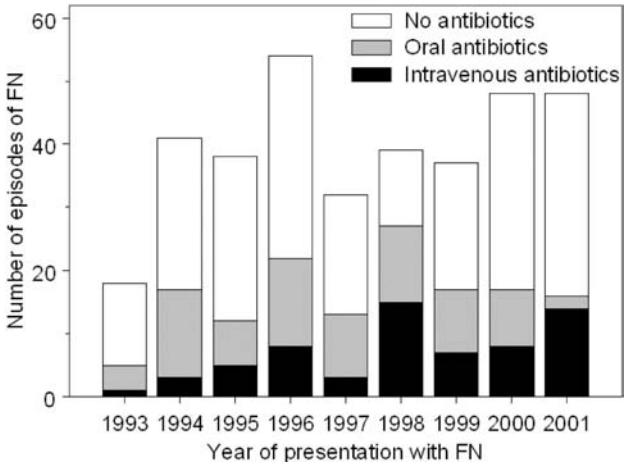

Fig. 2 Antimicrobial therapy at discharge after episode of fever in neutropenia (FN)

leukocyte counts $\leq 0.5\times10^9$/l, implying by definition an ANC $\leq 0.5\times10^9$/l. The other items of history, physical examination, and auxiliary examination recorded at presentation with FN did not change significantly over time.

Management

Patients were hospitalized in 361 (99.2%) episodes and treated with intravenous broad spectrum antibiotics in 356 (97.8%) of 364 episodes. In 337 (93%) of the episodes, the initial antimicrobial therapy was a combination of ceftriaxone plus amikacin [10]. This proportion remained stable (Table 3). The number of blood cultures performed per episode increased significantly, as was the proportion of episodes with at least one urine culture performed. The maximum value of the C-reactive protein increased over time. The median duration of hospitalization and of intravenous antimicrobial therapy, as well as the leukocyte and absolute neutrophil count at discharge, all remained stable over time. The proportion of patients discharged from hospital with continuing intravenous antimicrobial therapy in the outpatient setting, however, increased over time (Fig. 2).

Outcome

Two of 132 (1.5%) patients died because of infection, one in 1994, and one in 2001. There was a nonsignificant tendency towards increasing proportions of episodes with bacteremia in total, gram-negative bacteremia, bacteremia by CoNS, and bacteremia detected during administration of broad spectrum intravenous antimicrobial therapy (Table 4). In 28 (88%) of the 32 episodes with positive blood cultures taken during administration of broad spectrum intravenous antimicrobial therapy, CoNS was detected. *Pseudomonas aeruginosa* was detected twice in blood cultures, i.e., in 0.5% of the episodes and once in urine. Further details on the organisms causing bacteremia have been published elsewhere [5]. There were 19 clinically and/or microbiologically defined localized bacterial infections (ten skin and soft tissue, four head/neck/mouth, three phlebitis associated with peripheral venous catheter, and one each superinfected seroma and CNS). Their proportion remained stable over time. There were 21 microbiologically confirmed viral infections (eight influenza A, four respiratory syncytial virus, three parainfluenza, three herpes simplex virus 1, and one each mumps, enterovirus, and cytomegalovirus). Their proportion increased significantly during the study period. There was one case of suspected pulmonary aspergillosis.

Discussion

The evolution of the epidemiology of FN in a single center must be interpreted on the background of the evolution of the population treated with chemotherapy and thus being at risk to develop FN. The decrease over time of the absolute incidence of FN in patients with diagnoses other than PBC-ALL, with a constant relative

Table 4 Outcome. *FN* episode of fever in severe chemotherapy-induced neutropenia, *n.s.* not significant, i.e., p $\geq$0.01

Characteristic	Sample size	Overall proportion	Statistic	*p* value
Death due to infection	364	0.5%	0.00 [a]	n.s.
Bacteremia in total	364	24%	1.91 [a]	n.s.
Gram-negative bacteremia	364	8%	1.82 [a]	n.s.
Bacteremia by coagulase-negative staphylococci	364	11%	2.18 [a]	n.s.
Bacteremia during broad spectrum i.v. therapy	364	9%	2.02 [a]	n.s.
Polymicrobial bacteremia	364	3%	1.79 [a]	n.s.
Radiologically confirmed pneumonia	364	13%	[a]	n.s.
Localized bacterial infection	364	5%	0.25 [a]	n.s.
Microbiologically confirmed urinary tract infection	364	1.4%	1.39 [a]	n.s.
Microbiologically confirmed viral infection	364	6%	3.60 [a]	<0.001

[a] Standardized test statistic of the exact Cochrane-Armitage test for trend in binary data

incidence, reflects the decreasing number of these patients. This in turn is due to the fact that until 1996, patients from the other Swiss pediatric oncology centers were referred to Bern as the single Swiss center performing autologous bone marrow/peripheral blood stem cell transplantation. The stem cell mobilization regimen often led to FN. Episodes of FN caused by myeloablative therapy itself were not included in the study.

The increase over time of the intensity of chemotherapy applied [5, 6, 15] is reflected by (1) the increasing relative incidence of FN in patients with PBC-ALL irrespective of relapse status; (2) the increasing proportion of patients with other malignancies who had reached complete remission when presenting with FN; and (3) the decreasing leukocyte count at presentation. This is in line with the increased relative incidence of FN reported by others [15, 28]. The increased proportion of patients with central venous catheters presenting with FN simply reflects the more liberal indication to implant such a device, despite the well known risk of catheter-related infections by both gram-positive and gram-negative bacteria [2, 15, 27]. In contrast to other studies reporting on earlier periods [28], the proportion of patients receiving prophylactic G-CSF support did not increase significantly, because the indications for its use remained grossly unchanged since 1993.

As to management of the episodes of FN, diagnostic procedures like blood and urine cultures were performed with increasing frequency. This contrasts with the stable detection rate both of bacteremia and urinary tract infection. The present principle to repeat a set of blood cultures whenever the patient develops fever $\geq$38.5°C and/or shaking chills does not seem to be justified. The increasing maximum CRP levels probably reflect as well more frequent measurements (no data available). The increasing proportion of microbiologically confirmed viral infections reflects an increase in diagnostics as well (no data available). Viral diagnostics was performed when clinically indicated but with increasing frequency due to the increasing availability of sensitive and specific diagnostic methods. The increasing proportion of patients discharged from hospital with continuing intravenous antimicrobial therapy in the ambulatory setting was made possible by the development of pediatric home nursing. All other important topics of management remained unchanged. Despite the publication of two reports on small controlled [20] or uncontrolled [6] studies, the question of safety and efficacy of outpatient management and/or oral antimicrobial therapy in children and adolescents with FN at low risk for complications remained unresolved during the study period [13, 26]. Apart from rare exceptions, all patients were thus hospitalized and immediately treated with empirical intravenous broad-spectrum antimicrobial agents. The proportion of episodes of FN with bacteremia detected and the relative preponderance of gram-positive over gram-negative bacteremia were comparable to published results [2, 14, 27] and remained stable over time. The vast majority of bacteremia detected during administration of broad-spectrum intravenous antimicrobial therapy were caused by CoNS, which usually are not to life-threatening. Thanks to these facts and the low absolute incidence of *Pseudomonas aeruginosa* infections (incidence of bacteremia, 0.5%), there was no necessity to change the combination of ceftriaxone and amikacin [10] as empiric first-line antimicrobial therapy during the whole study period of 9 years. This is in line with the results from Gaslini's Children Hospital, Genova, Italy [15], and from the Alder Hey Children's Hospital in Liverpool, UK [21]. A multicenter surveillance study performed in 1995 in Italy [27] detected no major problem of antibiotic resistance either.

Our results contrast sharply, however, with the experiences reported from Innsbruck, Austria [28], where gram-negative bacteria increasingly resistant to the administered first-line antibiotic regimen became more prevalent, necessitating modifications of the antimicrobial strategy every 3 years between 1986 and 1995. Differences in the chemotherapeutic and antimicrobial therapy applied and microbiologic epidemiology may explain these contrasting results. Antimicrobial prophylaxis [9] beyond *P. jiroveci* pneumonia prophylaxis cannot explain this discrepancy, since it was not used in either center.

In contrast to other studies, only nonsignificant tendencies towards increasing proportions of episodes with

bacteremia [15, 28], gram-negative bacteremia [6, 15], and bacteremia by CoNS [15, 28] were detected. This may reflect true differences between the centers. Alternatively, it may be due to the smaller sample size leading to diminished power to detect changes.

An important number of the known components of risk prediction rules in FN such as type of malignancy [4, 5, 14, 18], intensity of chemotherapy [5], central venous catheter [4], presence of shaking chills [5, 18], and low leukocyte count [4, 5] corresponding partly to low absolute monocyte count (AMC) at presentation [8, 16, 19, 22], have changed significantly over time in this study. Risk prediction rules in pediatric FN thus should be updated regularly [12, 19].

This study has several limitations. (1) The retrospective study design leads to a few missing cases and many missing data, e.g., the systematically missing differentiation in leukocyte counts $\leq 0.5\times10^9$/l. (2) Repeated episodes of FN per patient were used for analysis without formally adapting the statistical tools to this situation. Since the median number of episodes per child was small and there were no important demographic differences between the first and the following episodes [4], the bias introduced is small and not clinically relevant, as has been shown in a different study [23]. (3) Direct comparison with most other studies is hampered by the temperature limits for defining fever, which are 0.5° higher than in most other centers but have proven to be safe in our division for more than a decade, i.e., they did not lead to an increased rate of children presenting with toxic appearance or of children dying from FN. (4) Episodes with one positive blood culture for CoNS were counted as bacteremia, though some other groups required at least two positive cultures for CoNS. This corresponds to our clinical practice where patients with at least one CoNS-positive blood culture and central venous catheters were treated with antimicrobial therapy in any case in order to minimize the risk of having to remove the catheter due to delayed start of therapy.

In conclusion, despite the limitations discussed, the major study results remain valid: The increasing relative incidence of FN reflects the increasing intensity of chemotherapy over time in pediatric oncology. In contrast to other centers, there was no necessity to modify the first-line antimicrobial therapy because of changing resistance patterns. Risk prediction rules in pediatric—and probably in adult—FN, need regular adaptation, since many of their components change significantly over time. In the future, prospective multicenter and ideally multinational studies surveying the evolution of FN may constitute an important topic of research with direct implications on the everyday management of this frequent complication.

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